Melchiorre Research Group

Group Leader: Paolo Melchiorre
Postdoctoral researchers: Yannick Rey / Bertrand Schweitzer-Chaput / John J. Murphy (until Sep.) / Luca Dell'Amico (until Aug.) / Charlie Verrier/Antoine Wallabregue (until Aug.) / Alberto Vega / Hamish Hepburn / Suva Paria (until Jul.) / Zhong-Yan Cao / Tamal Ghosh / Alexis Prieto
PhD students: Ana Bahamonde / Giacomo Filippini / Lukasz Wozniak / Luca Buzzetti / Sara Cuadros / Giandomenico Magagnano / Daniele Mazzarella / Pablo Bonilla
Visiting students: Maksim Ošeka
Laboratory technician: Eva Raluy
Administrative group coordinator: Lorna Piazzi

Abstract

The group's research interests are broadly based on the use of *enantioselective organocatalysis* (which involves only organic elements in the active principle) for the preparation of chiral molecules. Our strategy relies on the combination organocatalysis and visible light photocatalysis, two powerful strategies of modern chemical research with extraordinary potential for the sustainable preparation of organic molecules. The main focus is on the discovery and mechanistic elucidation of new enantioselective organocatalytic and photochemical processes that address unsolved problems in synthetic methodology. The final aim is to develop environmentally friendly and innovative catalytic methods that can find widespread use in modern organic synthesis.

Enantioselective Photo-organocatalysis

Our research aims at using visible light to promote synthetically useful synthetic processes. Our motivation is that using light excitation to bring a molecule from its ground state to an electronically excited state could open new dimensions for chemistry, since the reactivity of electronically excited molecules differs fundamentally from that in the ground state. The '*excited state reactivity*' could provide unexplored possibilities for developing processes that cannot be realised using thermal activation.

A central theme of modern stereoselective chemistry is the identification of strategies for exploring the unexpressed potential of enantioselective photocatalysis. In this context, our laboratory recently introduced a unique approach based on the ability of chiral enamines, key intermediates in thermal organocatalytic asymmetric processes, to actively participate in the photoexcitation of substrates while inducing the stereocontrolled formation of chiral products. The chemistry, which does not require the use of any external photoredox catalyst, provided access to useful chiral products that could not be synthesized by established ground-state enamine chemistry. We recently undertook extensive efforts to elucidate the key mechanistic aspects of such enantioselective photochemical α-alkylation of aldehydes. We established the potential of chiral enamines to directly participate in the photoexcitation of substrates either by forming a photoactive electron donor-acceptor (EDA) complex or by directly reaching an electronically excited state upon light absorption. These photochemical mechanisms generate radicals from closed-shell precursors under mild conditions. At the same time, the ground state chiral enamines provide effective stereochemical control over the enantioselective radical trapping process (Figure 1).

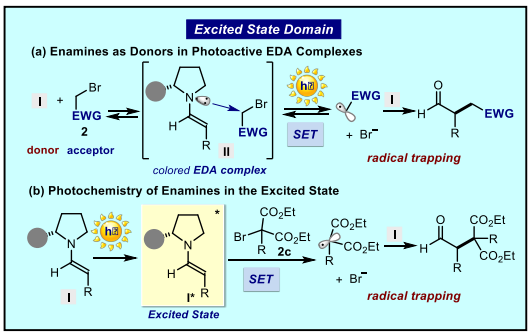

Figure 1. *Enantioselective α-alkylation of aldehydes: enamines can drive the photochemical generation of radicals by (**a**) inducing the formation of ground state, photoactive EDA complexes, and (**b**) acting as a photoinitiator upon direct light excitation. SET = single electron transfer; the grey circle represents the chiral organic catalyst scaffold.*

Then, we used a combination of conventional photophysical investigations, nuclear magnetic resonance (NMR) spectroscopy, and kinetic studies to gain a better understanding of the factors governing these enantioselective photochemical catalytic processes. Measurements of the quantum yield revealed that a radical chain mechanism is operative, while reaction-profile analysis and rate-order assessment indicated the trapping of the carbon-centered radical by the enamine, to form the carbon-carbon bond, as rate-determining. Our kinetic studies unveiled the existence of a delicate interplay between the light-triggered initiation step and the radical chain propagation manifold, both mediated by the chiral enamines (Figure 2).

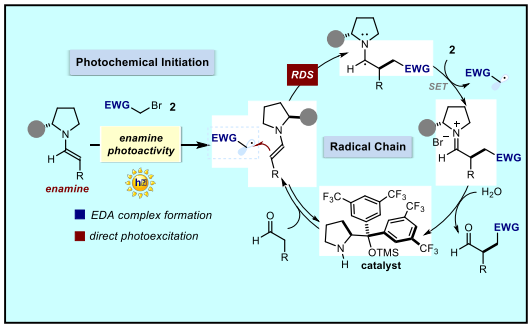

Figure 2. *The chain propagation underlying the mechanism od the asymmetric photochemical α-alkylation of aldehydes; J. Am. Chem. Soc.* ***2016****, 138, 8019-8030.*

In a different study, we evaluated the light excitation of 2-alkyl-benzophenones **1** to afford transient hydroxy-*o*-quinodinomethanes **A** (Figure 3). This is a historical photochemical process established in 1961. The unique reactivity of the generated photoenols **A**, which can act as dienes in [4+2]-cycloadditions with electron-poor alkenes **2**, generally provides a photochemical alternative to classical Diels-Alder chemistry, offering straightforward access to synthetically valuable benzannulated carbocyclic products. This historical light-triggered process has never before succumbed to an enantioselective catalytic approach. We demonstrated how asymmetric organocatalysis provides simple yet effective catalytic tools to

intercept photochemically generated hydroxy-o-quinodinomethanes **A** with high stereoselectivity. We used a chiral organic catalyst, derived from natural cinchona alkaloids, to activate maleimides **2** toward highly stereoselective Diels-Alder reactions. We uncovered an unconventional mechanism of stereocontrol, wherein the organocatalyst was actively involved in both the photochemical pathway, by leveraging the formation of the reactive photoenol, and the stereoselectivity-defining event.

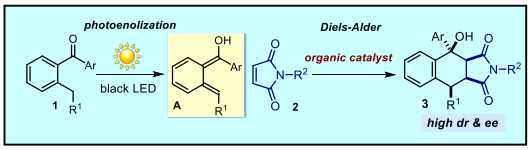

Figure 3. *Light excitation of 2-alkyl-benzophenones **1** affords transient hydroxy-o-quinodinomethanes **A**, reactive dienes suitable for [4+2]-cycloadditions. Because of its high reactivity and fleeting nature, **A** has never been trapped in a stereoselective catalytic fashion. We reported a simple organocatalytic strategy to control the stereochemical outcome of the Diels-Alder trapping of **A** with maleimides **2**, leading to stereochemically dense products **3**; Angew. Chem. Int. Ed. **2016**, 55, 3313-3317.*

Recently, we have developed a radical route to synthesise chiral quaternary carbons using light and organic catalysts. Many natural products and biologically active molecules contain chiral carbon atoms attached to four other carbons. Organic chemists can synthesize these quaternary stereocenters using organometallic reagents that add carbon groups to conjugated carbonyl compounds. These reagents, however, are expensive, can cause problematic side reactions, and don't always work well at crowded carbon centers. My research team has developed a new radical route to quaternary carbon stereocenters, offering a possibly easier approach to access such important chiral fragments.

Chemists previously have tried using radical-based conjugate addition reactions to form chiral quaternary centers. This is because, compared with organometallic reagents, radicals are intrinsically primed for connecting structurally congested carbons, are easier to produce, and cause less-problematic side reactions. But these radical reactions have not worked. For example, amine-catalyzed radical conjugate additions have been hampered by the formation of an unstable radical cation intermediate. My team has now found a way to circumvent this problem. In the reported amine-catalyzed reaction, we have used a novel electron-relay mechanism to bypass this unstable intermediate while preventing its breakdown (Figure 4). The result is the first enantioselective, catalytic, radical conjugate addition to generate quaternary carbon stereocenters.

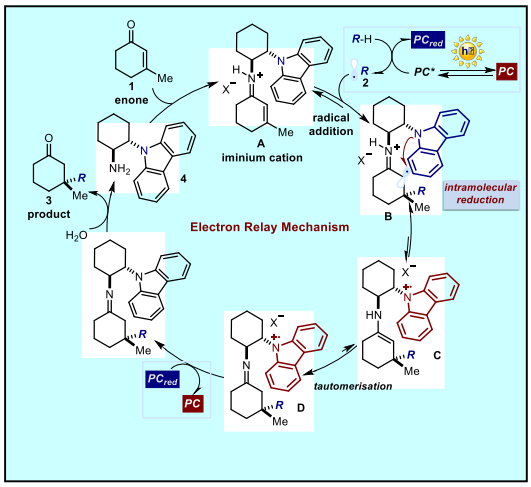

Figure 4. *The electron-relay mechanism for the construction of quaternary carbons by means of radical conjugate additions. Key to success was the design of a chiral organic catalyst **4**, adorned with a redox-active carbazole moiety, which drives the stereoselective interception of photochemically-generated carbon radicals **3**; X⁻ is an anion; **PC** is a photocatalyst; **PC*** is an excited photcatalyst; **PC**$_{red}$ is the reduced form; Nature **2016**, 532, 218-222.*

In the reaction, depicted in Figure 4, an organocatalyst's amine group condenses with an enone starting material **1** to produce a chiral iminium cation **A**. A radical carbon group **2** then adds to the carbon-carbon double bond in **A**, forming an unstable radical cation **B**. A redox-active carbazole group on the organocatalyst immediately reduces the unstable intermediate by intramolecular electron-transfer, preventing it from breaking down. The reduced intermediate **C** then easily forms a species **D** that is further reduced and hydrolyzed, yielding the quaternary product **3** and releasing the original organocatalyst **4**. A separate photocatalyst (**PC**) both creates the radical **3** and restore the redox-active carbazole group on the organocatalyst.

Articles

“Brønsted acid-catalysed conjugate addition of photochemically generated α-amino radicals to alkenylpyridines”
Chem. Commun. (**2016**) *52*, 3520–3523
Hamish B. Hepburn, Paolo Melchiorre

“Enantioselective Organocatalytic Diels–Alder Trapping of Photochemically Generated Hydroxy *o*-Quinodimethanes”
Angew. Chem. Int. Ed. (**2016**) *55,* 3313–3317
Luca Dell'Amico, Alberto Vega-Peñaloza, Sara Cuadros, Paolo Melchiorre

“Enantioselective Vinylogous Organocascade Reactions”
Chemical Record (**2016**) *16,* 1787–1806
Hamish B. Hepburn, Luca Dell'Amico, Paolo Melchiorre

“Mechanism of the Stereoselective α-Alkylation of Aldehydes Driven by the Photochemical Activity of Enamines”
J. Am. Chem. Soc. (**2016**) *138,* 8019-8030
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“Asymmetric catalytic formation of quaternary carbons by iminium ion trapping of radicals”
Nature (**2016**) *532*, 218–222
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